Electronically Filed

APPELLANTS' BRIEF	Attorney Docket No.	STAN-297
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	First Named Inventor	OMARY, M. BISHR
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Address to: Mail Stop AF Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Group Art Unit	1634
	Examiner Name	Myers, Carla J
	Title: "KERATIN 8 AND 18 MUTATIONS ARE RISK FACTORS FOR DEVELOPING LIVER DISEASE OF MULTIPLE ETIOLOGIES"	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated October 19, 2009. No claims have been allowed. Claims 1, 3, 6 and 7 are pending and appealed herein. A Notice of Appeal was filed on March 15, 2010. Accordingly, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815, reference no. STAN-297 to cover the fee required under 37 C.F.R. §1.17(b) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815, reference no. STAN-297.

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REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to the Board of Trustees of the Leland Stanford Junior University.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on July 27, 2006, with Claims 1-14. During the course of prosecution, Claim 15 was added, and Claims 2, 4, 5, and 8-14 were canceled. Claim 15 has been withdrawn by the Examiner. Accordingly, Claims 1, 3, 6 and 7 are pending in the present application, all of which stand rejected. All of the rejected claims are appealed herein.

STATUS OF AMENDMENTS

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to a method for detecting a predisposition to noncryptogenic liver disease, an increased risk for viral hepatitis or an increased risk for acute fulminant hepatitis in an individual human, comprising determining said predisposition by analyzing an individual human for a change in genotype of keratin relative to SEQ ID NO:4, wherein the change is associated with a predisposition to noncryptogenic liver disease and its progression, an increased risk for viral hepatitis or an increased risk for acute fulminant hepatitis and their progression in the individual human.

Below is a description of each appealed claim and where support for each can be found in the specification.

Claim 1 claims a method for detecting a predisposition to noncryptogenic liver disease comprising determining said predisposition by analyzing an individual human for a change in genotype of keratin relative to SEQ ID NO:4, wherein the change is selected from K18 Δ64-71; K18 T102A; K18 H127L; K18 I149V; K18 R260Q; K18 E275G; K18 Q284R; K18 T294M; K18 T296I; K18 G339R; K8 G52V; K8 Y53H; K8 G61C; K8 R340H; K8 G433S; K8 R453C; and K8 1-465(I)RDT(468), wherein the change is associated with a predisposition to noncryptogenic liver disease in the individual human (see specification at page 2, lines 1-8, page 5, lines 1-18, page 7, line 25 to page 8, line 10, and Table 3). Applicants note that the amino acid numbering listed herein (or the codon number) does not include the first amino acid of the translated protein, which is normally cleaved, as is readily understoof by one of skill in the art upon a comparison of the provided sequences and the known wild-type sequences.

Claim 3 claims a method for detecting a predisposition to an increased risk for viral hepatitis or acute fulminant hepatitis in an individual human, comprising determining said predisposition by analyzing nucleic acid of an individual human for a change in genotype relative to SEQ ID NO:4 at codon 340, wherein a mutation at codon 340 of keratin K8 from CGT→CAT is associated with a predisposition to increased risk for viral hepatitis or acute fulminant hepatitis in said individual human (see specification at page 2, lines 1-8, page 7, lines 25-31, and page 25, lines 10-23).

Claim 6 claims the method of Claim 3, wherein analyzing the nucleic acid comprises the steps of amplifying a region of keratin K8 coding sequences from isolated genomic DNA or mRNA to provide an amplified fragment, and detecting the presence of the change in genotype in the amplified fragment (see specification at page 8, lines 23-37, and page 9, line 13 to page 10, line 26).

Claim 7 claims the method of Claim 6, wherein the detecting step comprises hybridization with a probe specific for the change in genotype or digestion with specific restriction enzymes (see specification at page 8, lines 11-22 and page 10, lines 11-26).

Appellants note that Claim 1 has been objected to because the claim allegedly includes subject matter of the non-elected inventions. This objection can be timely addressed after the Appeal Brief has been considered.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 3, 6 and 7 stand rejected under 35 U.S.C. § 112, second paragraph. The Examiner has stated that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

II. Claim 1 stands rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement.

ARGUMENT

I. Claims 3, 6 and 7 have been rejected under 35 U.S.C. § 112, second paragraph.

With respect to the rejection under 35 U.S.C. § 112, second paragraph, the Appellants will argue the rejected claims in a single group.

The Examiner has rejected Claims 3, 6 and 7. It is asserted that it is unclear as to what is intended to be encompassed by "analyzing a nucleic acid for a genotype of an amino acid sequence or what is meant by a nucleic acid genotype relative to codon 340 of an amino acid sequence" (Final Office Action of 10/19/2009, p. 4).

The test for definiteness under 35 U.S.C. § 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576; 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986).

For the reasons detailed below, Appellants submit that Claims 3, 6 and 7 are definite under 35 U.S.C. § 112, second paragraph. Specifically, Appellants submit that one reasonably skilled in the art would understand what is claimed when the claim is read in light of the specification.

The rejected claims contain the element of a method for detecting a predisposition to increased risk for viral hepatitis or acute fulminant hepatitis in an individual human, comprising determining said predisposition by analyzing nucleic acid of an individual human for a change in genotype relative to a SEQ ID NO:4 at codon 340, wherein a mutation at codon 340 of keratin K8 from CGT→CAT is associated with a predisposition to increased risk for viral hepatitis or acute fulminant hepatitis in said individual human.

In making the rejection, the Examiner has asserted that the meaning of "analyzing nucleic acid of an individual human for a change in genotype relative to a SEQ ID NO:4 codon 340" is indefinite (Final Office Action of 10/19/2009, p. 4).

As the Office has acknowledged, SEQ ID NO:4 is the amino acid sequence of the K8 protein. Claim 3 recites a method which includes "analyzing nucleic acid... for a change in genotype

relative to SEQ ID NO:4 (the amino acid sequence of wild-type K8) at codon 340". In other words, the method includes analyzing the amino acid sequence of the nucleic acid which comprises the genotype to detect a change at codon 340 relative to the amino acid sequence of the nucleic acid which comprises the genotype of SEQ ID NO:4 at codon 340. A change in keratin K8 at codon 340 from CGT→CAT is associated with a predisposition to increased risk for viral hepatitis or acute fulminant hepatitis.

The Appellants contend that the meaning of the claim language is clear, in view of disclosed SEQ ID NO:4 and the specifically identified change in codon 340. One of ordinary skill in the art would clearly understand what is claimed when the claims are read in light of the specification.

Accordingly, Appellants respectfully submit that that one reasonably skilled in the art would understand what is claimed when the claim is read in light of the specification, and therefore Claims 3, 6, and 7 are definite under 35 U.S.C. § 112, second paragraph. The Appellants therefore respectfully request reversal of this rejection, and a timely Notice of Allowance be issued.

II. Claim 1 has been rejected under 35 U.S.C. § 112, first paragraph.

The Examiner has rejected Claim 1, because it asserted that the specification, while being enabling for methods for identifying a human subject at increased risk for viral hepatitis or acute fulminant hepatitis comprising (a) providing a nucleic acid sample from said human subject wherein the nucleic acid sample comprises a nucleic acid encoding keratin 8; (b) analyzing the sequence of the nucleic acid encoding keratin K8 to determine the identity of the nucleotides encoding codon 340; and (c) determining that said human subject has an increased risk for viral hepatitis or acute fulminant hepatitis if said human subject has the sequence CAT at codon 340 of the nucleic acid encoding keratin 8 as compared to a human subject that has the sequence CGT at codon 340 of the nucleic acid encoding keratin 8, allegedly does not reasonably provide enablement for methods for determining a predisposition to any noncryptogenic liver disease by determining a mutation in the keratin 8 gene resulting in a R340H substitution. The specification allegedly does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with the claim.

For the reasons detailed below, Appellants submit that Claim 1 is enabled under 35 U.S.C. § 112, first paragraph. Specifically, Appellants submit that one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The rejected claim contains the element of determining a predisposition to noncryptogenic liver disease by analyzing an individual human for a change in genotype of keratin relative to SEQ ID NO:4, wherein the change is selected from K18 Δ64-71; K18 T102A; K18 H127L; K18 I149V; K18 R260Q; K18 E275G; K18 Q284R; K18 T294M; K18 T296I; K18 G339R; K8 G52V; K8 Y53H; K8 G61C; K8 R340H; K8 G433S; K8 R453C; and K8 1-465(I)RDT(468), wherein the change is associated with a predisposition to noncryptogenic liver disease in the individual human.

In making the rejection, the Examiner has asserted that "neither the 132 declaration nor the response provide any arguments or evidence to establish that the findings obtained with acute liver failure can be extrapolated to the genus of noncryptogenic liver diseases" (Final Office Action of 10/19/2009, p. 6, emphasis original).

In response, Appellants respectfully submit that Claim 1 meets the requirements of 35 U.S.C. 112, first paragraph.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[2]

The instant specification teaches multiple mutations, both in keratin K8 and in K18, that are associated with liver disease, as shown in Tables 3 and 4, which mutations cover a number of different residues in these proteins. It is noted that many of these mutations have an underlying molecular logic, in that there is a destabilization of the protein, providing for a logical nexus between genetic defect and disease. As cited in Ku, et al. (*Keratin Mutations Predispose to Cryptogenic and and Noncryptogenic Liver Disease*; Gastroenterology, 2002), there is an "extensive body of

1 *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

2 *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

transgenic animal data showing that keratins play an essential role in protecting hepatocytes from mechanical and nonmechanical stresses".

Therefore, the Appellants contend that the specification clearly discloses evidence that keratins play an essential role in protecting hepatocytes from stresses, and clear evidence that the mutations recited in the claims are associated with a number of noncryptogenic liver diseases.

For example, Table 6 shows the molecular consequences of keratin mutations:

Table 6. Molecular Consequences of Keratin mutations

Mutations		Potential effects
K8	**R340H**	Destabilization
	G433S	Altering keratin phosphorylation
	R453C	Formation of a disulfide bond
	1-465(I) RDT(468)	Destabilization
K18	**Δ 64-71(TGIAGGLA)**	Destabilization
	E275G	Destabilization
	Q284R	Destabilization
	T294M	Interruption of ionic interaction
	T296I	Interruption of ionic interaction

The Examiner has asserted that Table 6 "does not indicate what is destabilized" and that "the specification and response do not explain why this potential effect of destablilization would be expected to cause or otherwise be associated with a representative number of noncryptogenic liver diseases" (Final Office Action of 10/19/2009, pp. 7-8, emphasis original).

However, the Appellants contend that the specification does disclose that destabilizing effects of the keratin mutations can include destabilizing K8/K18 filaments, interrupting ionic interactions, introducing disulfide bonds, or altering keratin phosphorylation/solubility, as recited in paragraph 84 of the specification, reproduced below:

> At the molecular level mutations in IF chains can, in principle, alter the α-helical propensity of the chains, the number and type of the intra- and inter-helical ionic interactions,

increase or decrease the stability of the α-helical strands, modify the helix capping potential and change the hydrogen bonding ability of the chains. Mutations could also adversely affect the ability of the molecules to assemble in to viable IF, to bundle as normally required, or to function properly even if assembled correctly (Table 6). Therefore, potential effects of the keratin mutations include destabilizing K8/K18 filaments, interrupting ionic interactions, introducing disulfide bonds, or altering keratin phosphorylation/solubility. These molecular consequences of keratin mutations may interfere the normal filament reorganizations that occur in hepatocytes upon multiple physiologic and nonphysiologic stimuli, and ultimately result in liver disease (Fig. 6).

Additionally, the inventors have presented specific studies demonstrating that K8/K18 proteins protect hepatocytes from a variety of stresses. For example, the authors have shown that cytoplasmic filament organization is abnormally altered after stress exposure with K8 Y53H/G61C mutations, as recited in the paragraph 87 of the specification, reproduced below (emphasis added):

> "...multiple transgenic mouse model studies showed that K8/K18 serve the essential function of protecting hepatocytes from a variety of stresses including agents that cause acute (e. g. acetaminophen) or chronic (e. g. griseofulvin) injury, and agents that induce apoptosis (e. g. Fas antibody). K8/K18 may also be involved in protein targeting to the apical compartment of polarized epithelia, interacting with apoptotic machinery proteins, cell signaling and regulating the availability of abundant cellular proteins. Hence, keratin mutations may potentially act at a number of functional cellular nodes. One surrogate marker of keratin function is cytoplasmic filament organization, which was shown to be abnormally altered, only after stress exposure, in the K8 Y53H/G61C mutations (Ku et al, N Engl J Med 344: 1580-1587, 2001).

The inventors have also demonstrated in animal models a clear association between the K8 G62C and R341H mutations and liver damage, as documented on page 7 of the previously submitted Declaration under 37 C.F.R. §1.132, reproduced below (emphasis added):

> **K8 R341H Mice are More Susceptible to APAP-Induced ALF:** In order to further substantiate the importance of K8 R341H in human ALF, we generated transgenic mice that express human K8 R341H and tested their susceptibility to APAP-induced liver injury. Expression of the human K8 transgene was confirmed biochemically. As controls, we used mice that express WT human K8, or mice that express human K8 G62C which is also found in some ALF patients, and predisposes to apoptotic liver injury induced by Fas ligand. Human K8 protein expression was comparable in the three genotypes and there was no evidence of liver pathology under basal conditions. However, APAP challenge led to more prominent liver injury (necrosis, hemorrhage, serologic hepatitis) in the K8 G62C and R341H genotypes as compared with K8 WT.

Applicants note the numbering of the amino acids in the mutations, which as described above refer to the mature protein which lacks the terminal methionine that is normally cleaved.

In addition to presenting evidence that keratins play an essential role in protecting hepatocytes from stresses, the Appellants have clearly linked K8/K18 mutations to keratin-associated liver diseases.

For example, the present application discloses that K8 Y53H, K8 G61C, and most prominently K8 R340H are shown to be mutation hot spots in a significant number of patients with keratin-associated liver diseases. The Appellants have also shown a clearly documented increase in K8 and K18 mutations in patients with noncryptogenic liver diseases, as compared to controls (see specification, para 76):

> The mutations that were identified in 58 of 467 patients represent a mutation frequency of 12.4%, as compared with a mutation frequency of 3.7% found in 13 of 349 controls ($P<0.0001$; Tables 3 and 4).

The evidence presented also supports the conclusion that the claimed K8/K18 mutations result in a fundamental injury which can result in disease, in that in some cases, a single K8/K18 mutation can be associated with more than one keratin-associated liver disease. For example, as presented in Tables 4 and 5, the R340H keratin mutation is associated with fulminant hepatic failure, hepatitis B and C, alcoholic disease, and biliary atresia. The K8 Y53H mutation is linked to both viral hepatitis and biliary atresia. The K8 G61C mutation is associated with viral hepatitis, alcoholic disease, and cystic fibrosis. The K18 Δ64-71 mutation is linked to both hepatitis C and alcoholic disease, etc.

The Appellants have also submitted data from the present inventors regarding the importance of keratin 8 variants in acute liver failure and the importance of some K8 variants in African Americans with liver disease and in African Americans in general. As disclosed in the previously submitted Declaration under 37 C.F.R. §1.132 on page 9 (emphasis added):

> "The overall frequency of biologically-relevant K8/K18 variants in our cohort (13.1%) was similar to that in patients with chronic end-stage liver disease (13.4%), but significantly higher than in blood-bank donors (3.7%). This highlights the importance of *KRT8/KRT18* gene variants in both acute and chronic liver disease."

The Appellants note that the findings presented in the 132 Declaration are directed to the R341H K8 mutation, as opposed to the R340H mutation in the present claims. Examination of the SEQ ID NO:4 sequence listing shows that the K8 R341H mutation referred to the in Declaration under 37 C.F.R. §1.132 and the K8 R340H mutation referred to in current specification refer to the same mutation, and that this difference can be accounted for by difference in numbering convention. The change in numbering is consistent, as for example, the codon labeled K8 G433S in the specification is referred to as K8 G434S in the Declaration, etc., and merely refers to the mature protein v. the unprocessed form that contains a terminal methionine.

Appellants respectfully submit that the specification and the claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation. Relevant enablement factors are discussed in detail below.

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[3]

As the court explained[4]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art, which routinely performs such long experiments.[5]

The claimed methods relate to the use of the many different polymorphisms for keratin K8 and K18 that are provided in the application. The sequence of polynucleotides is determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on different samples. Since these experiments are empirical in nature, no undue experimentation is required. In other words, the only

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3 See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
4 *In re Wands* 8 USPQ 2d at 1404
5 *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay to determine the active variants, no undue experimentation is necessary.

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[6] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[7] As discussed above, numerous working examples have been provided.

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with the equivalent of a doctoral degree in molecular biology techniques, although Appellants believe that a much lower skill level would be sufficient to perform the claimed methods. Furthermore, such technicians are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing cell-based assays is high.

There may be some non-functional variants within the genus defined by the claims. However, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work.

The court has very clearly explained[8]:

> "To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

In sum, the amount of experimentation required to practice the methods of the invention would not be undue because a) a working example has been provided, b) guidance is given on how to test the sequences has been provided, and c) one of skill in the art would be able to perform the experiments as a matter of routine to determine the sequences.

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6 In re Borkowski, 164 USPQ at 645.
7 *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).
8 *In re Angstadt*, 190 USPQ at 218.

The Office Action has stated that "it is well-recognized in the art that associations between polymorphisms and phenotypic traits are often irreproducible". Appellants submit that the present invention is based not only on human association studies, but on supporting animal models that are reflective of human disease. Further, the use of association studies is well-supported in guiding human health decisions. For example, the odds ratio for liver failure associated with the genetic markers of the present invention is higher than the odds ratio for the well-known association of smoking and heart disease.

Therefore, the Appellants contend that in view of extensive data confirming that keratins play an essential role in protecting hepatocytes from stresses, and clear evidence that the mutations recited in the claims are associated with a number of noncryptogenic liver diseases, the specification does clearly enable methods for determining a predisposition to noncryptogenic liver disease by analyzing an individual human for a change in genotype of keratin relative to SEQ ID NO:4, wherein the change is associated with a predisposition to noncryptogenic liver disease.

In fact, the Appellants contend that the Office has not provided sufficient evidence to support the assertion that the claims are not enabled. When rejecting a claim as non-enabled, the examiner bears the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Appellants further submit that the recent Board decision, Appeal 2009-0938, *Ex parte Xu et al.*, is relevant to the facts of the present application.

The Appellants therefore contend that in view of the extensive evidence presented in the specification that keratins play an essential role in protecting hepatocytes from stresses, and clear evidence that the mutations recited in the claims are associated with a number of noncryptogenic liver diseases, the Office has failed to provide a sufficient reason to suggest that the claims are not enabled.

In view of the discussion above, Appellants respectfully submit that that one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation, and therefore Claim 1 is enabled under 35 U.S.C. § 112, first paragraph. The Appellants therefore respectfully request reversal of this rejection, and a timely Notice of Allowance be issued in this case.

SUMMARY

The Appellants' claims are directed to detecting a predisposition to noncryptogenic liver disease or to poor liver disease prognosis comprising analyzing an individual human for a change in genotype of keratin relative to SEQ ID NO:4, wherein the change is associated with a predisposition to increased risk for noncryptogenic liver disease.

The Appellants contend that Claims 3, 6 and 7 are definite under 35 U.S.C. § 112, second paragraph. The meaning of the claim language is clear, in view of the specific disclosure of SEQ ID NO:4, and the clearly identified change in codon 340 of keratin 8. The Appellants contend that one of ordinary skill in the art would clearly understand what is claimed when the claims are read in light of the specification.

The Appellants further contend that Claim 1 is enabled under 35 U.S.C. § 112, first paragraph. The Appellants have provided extensive evidence to support the association between K8 and K18 mutations and a predisposition to noncryptogenic liver disease, as discussed above. Further, as the relevant ordinarily skilled artisan is generally a skilled laboratory technician with the equivalent of a doctoral degree ,or possibly less, in molecular biology techniques, the practitioner need only perform very routine experiments to determine whether a polynucleotide meets the requirements of the claims. The Appellants contend that one of ordinary skill in the art could make or use the invention from the disclosures in the specification coupled with information known in the art without undue experimentation, and therefore, Claim 1 is enabled under 35 U.S.C. § 112, first paragraph

In view of the arguments above, Appellants respectfully request reversal of the rejections.

RELIEF REQUESTED

The Appellants respectfully request that the rejection of Claims 3, 6, and 7 under 35 U.S.C. § 112, second paragraph, and the rejection of Claim 1 under 35 U.S.C. § 112, first paragraph be reversed; and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: May 14, 2010

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CLAIMS APPENDIX

1. A method for detecting a predisposition to noncryptogenic liver disease in an individual human, the method comprising:

determining said predisposition to noncryptogenic liver disease by analyzing an individual human for a change in genotype of keratin relative to SEQ ID NO:4, wherein said change is selected from K18 Δ64-71; K18 T102A; K18 H127L; K18 I149V; K18 R260Q; K18 E275G; K18 Q284R; K18 T294M; K18 T296I; K18 G339R; K8 G52V; K8 Y53H; K8 G61C; K8 R340H; K8 G433S; K8 R453C; and K8 1-465(I)RDT(468),

wherein the change is associated with a predisposition to noncryptogenic liver disease in said individual human.

3. A method for detecting a predisposition to increased risk for viral hepatitis or acute fulminant hepatitis in an individual human, the method comprising:

determining said predisposition by analyzing nucleic acid of an individual human for a change in genotype relative to a SEQ ID NO:4 at codon 340,

wherein a mutation at codon 340 of keratin K8 from CGT→CAT is associated with a predisposition to increased risk for viral hepatitis or acute fulminant hepatitis in said individual human.

6. The method of Claim 3, wherein said analyzing the nucleic acid comprises the steps of:

amplifying a region of keratin K8 coding sequences from isolated genomic DNA or mRNA to provide an amplified fragment;

detecting the presence of said change in genotype in said amplified fragment.

7. The method of Claim 6, wherein said detecting step comprises hybridization with a probe specific for said change in genotype or digestion with specific restriction enzymes.

EVIDENCE APPENDIX

Declaration under 37 C.F.R. §1.132 (executed by Bishr Omary) submitted with the Response to Office Action of 8/10/2009, filed with the USPTO on August 28, 2009.

Ku, et al., *Keratin Mutations Predispose to Cryptogenic and Noncryptogenic Liver Disease*; Gastroenterology, 2002, and Ku et al, *Keratin Mutations in Patients with Cryptogenic Liver Disease*; N Engl J Med 344: 1580-1587, 2001cited in IDS, filed with the USPTO on November 17, 2005.

Ex parte Xu, submitted to the USPTO with the Response to Office Action and filed with the USPTO on August 28, 2009.

RELATED PROCEEDINGS APPENDIX

none